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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) **International Patent Classification** 6 : **C12N 15/00**

A3

(11) **International Publication Number:** **WO 95/10628**

(43) **International Publication Date:** 20 April 1995 (20.04.95)

(21) **International Application Number:** PCT/US94/10090

(22) **International Filing Date:** 9 September 1994 (09.09.94)

(30) **Priority Data:**
08/128,971 28 September 1993 (28.09.93) US

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(81) **Designated States:** CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(88) **Date of publication of the international search report:**
19 September 1996 (19.09.96)

(54) **Title:** SIGNAL TRANSDUCTION VIA CD28

(57) **Abstract**

Disclosed are compositions and methods of blocking T cell signal transduction by introducing into a T cell a peptide comprising a PI 3-kinase-binding-sequence which decreases the association of PI 3-kinase with CD28. Also disclosed are compositions and methods of amplifying T cell activation by introducing into a T cell, a plurality of modified T cell surface proteins, the cytoplasmic tail of which comprises a plurality of copies of a PI 3-kinase-binding-sequence.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10090

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C12N 15/00
US CL :800/2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 800/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG, CD28, cytoplasmic tail, PI-3 kinase binding sequence

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Immunology, Volume 149, No. 1, issued 01 July 1992, Lu et al., "CD28-induced T cell Activation: Evidence for a protein-tyrosine kinase signal transduction pathway", pages 24-29, see entire article.	1, 2, 7-10
Y	Proceedings of the National Academy of Sciences USA, Volume 84, issued December 1987, Aruffo et al., "Molecular cloning of a CD28 cDNA by a high-efficiency COS cell expression system", pages 8573-8577, see entire article.	1, 2, 7-10
Y	Cell, Volume 71, No. 3, issued 30 October 1992, Pawson et al., "SH2 and SH3 domains: From structure to function", pages 359-362, see entire article.	1, 2, 7-10

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 09 NOVEMBER 1994	Date of mailing of the international search report DEC 30 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SUZANNE ZISKA, PH.D. Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

Inte...ational application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Science, Volume 260, issued 14 May 1993, Tuveson et al., "CD19 to B cells as a surrogate kinase insert region to bind phosphatidylinositol 3-kinase", pages 986-989, see entire article.	1, 2, 7-10
Y	Cell, Volume 69, issued 01 May 1992, Fantl et al., "Distinct phosphotyrosines on a growth factor receptor bind to specific molecules that mediate different signaling pathways", pages 413-423, see entire article.	1, 2, 7-10

INTERNATIONAL SEARCH REPORT

Inte ational application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 7-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10090

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I. Claims 1, 2 and 7-10, drawn to a method of modulating signal transduction in T cells, which method comprises introducing into a T cell a peptide which decreases the association of PI 3-kinase with CD28, wherein said peptide comprises a PI 3-kinase binding fragment of the cytoplasmic tail of CD28, and claims 7-10, drawn to a modified T cell surface protein comprising a cytoplasmic tail comprising a plurality of copies of a PI-3 kinase binding sequence, classified in Class 530, subclass 350, for example,and classified in Class 435, subclass 240.2, for example.

Group II. Claims 3 and 4, drawn to a modified CD28 molecule lacking a portion of the cytoplasmic tail of wild type CD28, classified in Class 530, subclass 350, for example.

Group III. Claims 5 and 6, drawn to a DNA encoding the modified CD28 of claim 4 and a cell expressing the DNA, classified in Class 536, subclass 23.5, for example.

Group IV. Claims 11 and 12, drawn to a DNA encoding the protein of claim 10 and a cell expressing the DNA, classified in Class 536, subclass 23.5, for example.

Group V. Claims 13 and 14, drawn to a DNA encoding a protein wherein said protein is CD3 modified to comprise a plurality of copies of SEQ. ID NO:1 in its cytoplasmic tail, classified in Class 536, subclass 23.5, for example.

Group VI. Claims 15 and 16, drawn to a DNA encoding a protein wherein said protein is CD7 modified to comprise a pluralityofcopies of SEQ. ID NO:1 in its cytoplasmic tail, classified in Class 536, subclass 23.5, for example.

Group VII. Claims 17 and 18, drawn to a DNA encoding a protein wherein said protein is CTLA-4 modified to comprise a plurality of copies of SEQ. ID NO:1 in its cytoplasmic tail, classified in Class 536, subclass 23.5, for example.

Group VIII. Claims 19 and 20, drawn to a method of amplifying signal transduction in a T cell, classified in Class 435, subclass 244, for example.

Group IX. Claims 21-23, drawn to a method of screening candidate compounds to identify a compound capable of modulating the association of CD28 with PI 3-kinase, classified in Class 435, subclass 7.1, for example.

Group X. Claims 24-27, drawn to a transgenic non-human mammal, having a transgene encoding a modified T cell surface protein comprising a cytoplasmic tail comprising a plurality of copies of a PI-3 kinase binding amino acid sequence, classified in Class 800, subclass 2, for example.

The inventions listed as Groups I-X do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Inventions II-X are drawn to multiple uses and products not encompassed by Invention I. PCT Rules 13.1 and 13.2 do not permit multiple distinct products and methods within a single application. For example, Inventions II-VII and X lack unity as they are directed to distinct products such as DNA, proteins and transgenic animals. Inventions II-VII and X are different and distinct since each product has different characteristics necessitating separate searches. Inventions VIII and IX lack unity as they are directed to distinct methods of using the multiple products as listed above. The methods of Inventions VIII and IX use independent and different starting materials, have different steps and conditions which are distinct and not obvious variants of each other.

Accordingly, the claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.